1.3. FOURIER TRANSFORMS IN CRYSTALLOGRAPHY

– for each type of atom $j \in J$, since the coefficients of the differential synthesis must be multiplied by $g_j(\mathbf{h})$.

Agarwal disposed of the latter dependence by pointing out that the multiplication involved is equivalent to a real-space *convolution* between the differential synthesis and $\sigma_j(\mathbf{x})$, the standard electron density ρ_j for atom type j (Section 1.3.4.2.1.2) smeared by the isotropic thermal agitation of that atom. Since σ_j is *localized*, this convolution involves only a small number of grid points. The requirement of a distinct differential synthesis for each parameter type, however, continued to hold, and created some difficulties at the FFT level because the symmetries of differential syntheses are more complex than ordinary space-group symmetries. Jack & Levitt (1978) sought to avoid the calculation of difference syntheses by using instead finite differences calculated from ordinary Fourier or difference Fourier maps.

In spite of its complication, this return to the Fourier implementation of the least-squares method led to spectacular increases in speed (Isaacs & Agarwal, 1978; Agarwal, 1980; Baker & Dodson, 1980) and quickly gained general acceptance (Dodson, 1981; Isaacs, 1982a,b, 1984).

1.3.4.4.7.7. *Lifchitz's reformulation*

Lifchitz [see Agarwal *et al.* (1981), Agarwal (1981)] proposed that the idea of treating certain multipliers in Cruickshank's modified differential Fourier syntheses by means of a convolution in real space should be applied not only to $g_j(\mathbf{h})$, but also to the polynomials $P_p(\mathbf{h})$ which determine the type of differential synthesis being calculated. This leads to convoluting $\partial\sigma_j/\partial u_p$ with the *same* ordinary weighted difference Fourier synthesis, rather than σ_j with the differential synthesis of type p. In this way, a *single* Fourier synthesis, with *ordinary* (scalar) symmetry properties, needs be computed; the parameter type and atom type both intervene through the function $\partial\sigma_j/\partial u_p$ with which it is convoluted. This approach has been used as the basis of an efficient general-purpose least-squares refinement program for macromolecular structures (Tronrud *et al.*, 1987).

This rearrangement amounts to using the fact (Section 1.3.2.3.9.7) that convolution commutes with differentiation. Let

$$D(\mathbf{x}) = \sum_{\mathbf{h}} w_{\mathbf{h}}(|F_{\mathbf{h}}^{\mathrm{calc}}| - |F_{\mathbf{h}}|^{\mathrm{obs}}) \exp(i\varphi_{\mathbf{h}}^{\mathrm{calc}}) \exp(-2\pi i\mathbf{h} \cdot \mathbf{x})$$

be the inverse-variance weighted difference map, and let us assume that parameter u_p belongs to atom j. Then the Agarwal form for the pth component of the right-hand side of the normal equations is

$$\left(\frac{\partial D}{\partial u_p} * \sigma_j\right)(\mathbf{x}_j),$$

while the Lifchitz form is

$$\left(D * \frac{\partial \sigma_j}{\partial u_p}\right)(\mathbf{x}_j).$$

1.3.4.4.7.8. *A simplified derivation*

A very simple derivation of the previous results will now be given, which suggests the possibility of many generalizations.

The weighted difference map $D(\mathbf{x})$ has coefficients $D_{\mathbf{h}}$ which are the gradients of the global residual with respect to each $F_{\mathbf{h}}^{\mathrm{calc}}$:

$$D_{\mathbf{h}} = \frac{\partial R}{\partial A_{\mathbf{h}}^{\mathrm{calc}}} + i\frac{\partial R}{\partial B_{\mathbf{h}}^{\mathrm{calc}}}.$$

By the chain rule, a variation of each $F_{\mathbf{h}}^{\mathrm{calc}}$ by $\delta F_{\mathbf{h}}^{\mathrm{calc}}$ will result in a variation of R by δR with

$$\delta R = \sum_{\mathbf{h}} \left[\frac{\partial R}{\partial A_{\mathbf{h}}^{\mathrm{calc}}}\delta A_{\mathbf{h}}^{\mathrm{calc}} + \frac{\partial R}{\partial B_{\mathbf{h}}^{\mathrm{calc}}}\delta B_{\mathbf{h}}^{\mathrm{calc}}\right] = \mathscr{R}e \sum_{\mathbf{h}}[\overline{D_{\mathbf{h}}}\delta F_{\mathbf{h}}^{\mathrm{calc}}].$$

The $\mathscr{R}e$ operation is superfluous because of Friedel symmetry, so that δR may be simply written in terms of the Hermitian scalar product in $\ell^2(\mathbb{Z}^3)$:

$$\delta R = (\mathbf{D}, \delta\mathbf{F}^{\mathrm{calc}}).$$

If ρ^{calc} is the transform of $\delta\mathbf{F}^{\mathrm{calc}}$, we have also by Parseval's theorem

$$\delta R = (D, \delta\rho^{\mathrm{calc}}).$$

We may therefore write

$$D(\mathbf{x}) = \frac{\partial R}{\partial\rho^{\mathrm{calc}}(\mathbf{x})},$$

which states that $D(\mathbf{x})$ is the functional derivative of R with respect to ρ^{calc}.

The right-hand side of the normal equations has $\partial R/\partial u_p$ for its pth element, and this may be written

$$\frac{\partial R}{\partial u_p} = \int_{\mathbb{R}^3/\mathbb{Z}^3} \frac{\partial R}{\partial\rho^{\mathrm{calc}}(\mathbf{x})} \frac{\partial\rho^{\mathrm{calc}}(\mathbf{x})}{\partial u_p}\mathrm{d}^2\mathbf{x} = \left(D, \frac{\partial\rho^{\mathrm{calc}}}{\partial u_p}\right).$$

If u_p belongs to atom j, then

$$\frac{\partial\rho^{\mathrm{calc}}}{\partial u_p} = \frac{\partial(\tau_{\mathbf{x}_j}\sigma_j)}{\partial u_p} = \tau_{\mathbf{x}_j}\left(\frac{\partial\sigma_j}{\partial u_p}\right);$$

hence

$$\frac{\partial R}{\partial u_p} = \left(D, \tau_{\mathbf{x}_j}\left(\frac{\partial\sigma_j}{\partial u_p}\right)\right).$$

By the identity of Section 1.3.2.4.3.5, this is identical to Lifchitz's expression $(D * \partial\sigma_j/\partial u_p)(\mathbf{x}_j)$. The present derivation in terms of scalar products [see Brünger (1989) for another presentation of it] is conceptually simpler, since it invokes only the chain rule [other uses of which have been reviewed by Lunin (1985)] and Parseval's theorem; economy of computation is obviously related to the good localization of $\partial\rho^{\mathrm{calc}}/\partial u_p$ compared to $\partial F^{\mathrm{calc}}/\partial u_p$. Convolutions, whose meaning is less clear, are no longer involved; they were a legacy of having first gone over to reciprocal space *via* differential syntheses in the 1940s.

Cast in this form, the calculation of derivatives by FFT methods appears as a particular instance of the procedure described in connection with variational techniques (Section 1.3.4.4.6) to calculate the coefficients of local quadratic models in a search subspace; this is far from surprising since varying the electron density through a variation of the parameters of an atomic model is a particular case of the 'free' variations considered by the variational approach. The latter procedure would accommodate in a very natural fashion the joint consideration of an energetic (Jack & Levitt, 1978; Brünger *et al.*, 1987; Brünger, 1988; Brünger *et al.*, 1989; Kuriyan *et al.*, 1989) or stereochemical (Konnert, 1976; Sussman *et al.*, 1977; Konnert & Hendrickson, 1980; Hendrickson & Konnert, 1980; Tronrud *et al.*, 1987) restraint function (which would play the role of S) and of the crystallographic residual (which would be C). It would even have over the latter the superiority of affording a genuine *second-order* approximation, albeit only in a subspace, hence the ability of detecting negative curvature and the resulting bifurcation behaviour (Bricogne, 1984). Current methods are unable to do this because they use only *first-order* models, and this is known to degrade severely the overall efficiency of the refinement process.